

BNSDOCID: <WO 0125243A1_1_1>

CARBON MONOXIDE SOURCE FOR THE PREPARATION OF
TRANSITION METAL CARBONYL COMPLEXES

The present invention relates to compounds that have a novel use as a carbon monoxide source and optionally as a reducing agent in the preparation of transition metal carbonyl complexes.

5 Carbonyl complexes are compounds that contain carbon monoxide as a coordinated ligand. Carbon monoxide is a common ligand in transition metal chemistry, in part due to the synergistic nature of its bonding to transition metals.

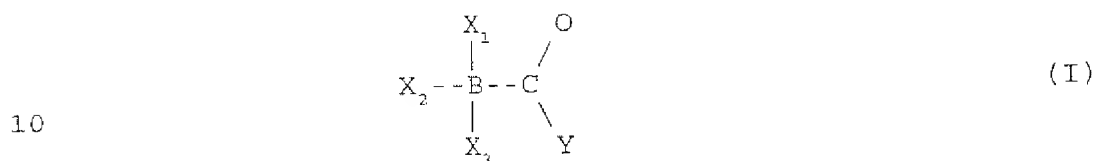
10 The bonding of CO to a metal consists of two components. The first component of the bonding is based on σ -donation, the overlap of a lone pair on the carbon atom with an empty d-orbital of the metal. The second component consists in π -back-donation from a filled d-
15 orbital of the metal into an empty π^* orbital of the carbon atom of CO. This second component is called pi-backbonding or pi-backdonation.

The above described formation of carbonyl complexes with transition metals is crucial for the
20 application of such compounds in the labeling of proteins, peptides and a variety of other compounds. For many applications these molecules are labeled by means of a so-called labeling kit which contains the necessary reagents. Current kits are based on boron hydride as the
25 reducing agent, further contain tartrate, lactose and borate buffer, pH 11.5, and are filled with gaseous CO as the CO source. The disadvantages of these known reaction mixtures are the slow dissolution of CO into the reaction solvent resulting in a decreased yield of carbonyl
30 complexes, the impossibility of industrial preparation of large amounts of CO filled kit vials and the slow diffusion of CO even through tightly closed vials. Moreover, the pH is rather high, which is not convenient.

It is the object of the present invention to provide an alternative for CO and sodium boron hydride that does not have the above stated drawbacks.

It has now been found that compounds of formula

5 I



wherein:

X_1 is -H;

15 X_2 and X_3 are substituents which may be the same or different and are selected from the group consisting of -H, $-NH_xR_y$ with $x+y=3$, or -R, wherein R is a substituent which is bound by a carbon atom to the nitrogen or boron, respectively, and is preferably alkyl or aryl;

20 Y is -OH, $-OH_2$, -OR or -NHR, wherein R is a substituent which is bound by a carbon atom to the nitrogen or oxygen, respectively, and is preferably alkyl or aryl; or salts thereof

can be used as a carbon monoxide (CO) source and

25 optionally also as a reducing agent in the preparation of metal carbonyl complexes in aqueous solution. If Y is -OH or $-OH_2$, the compounds are acids which can be deprotonated (i.e. with NaOH). In that case, the compounds which are isolated are the salts (borano carbonate anion R_3B-COO^{2-} plus the corresponding cation, e.g. Li^+ , Na^+ , Ca^{2+} , Mg^{2+} and
30 others). The reducing agent function is only present if at least one of X_1 , X_2 and X_3 is a hydrogen. For stability reasons it is preferred that two of X_1 , X_2 and X_3 are -H. The carbon monoxide is released upon heating an aqueous
35 solution of the compound.

The advantages of the above compounds are the following. CO is produced for the first time in aqueous media under controllable conditions (pH, temperature).

Carbonyl complexes of the claimed metals can be prepared
40 in water at well defined conditions instead of organic

solvents or under high pressure and high temperature. The CO source and reducing agent can be present in the same single compound, which is convenient since reduction is practically always required for the preparation of
5 carbonyls. In case the metal to be complexed is Tc-99m or Re-188/186 kits can be produced without the demand of filling a vial with toxic and volatile CO. A major advantageous embodiment is a molecule combining the different functionalities in one compound. Such compound
10 can act as a reducing agent and as an in situ CO source, where the CO is only produced if a protic solvent (like water) or a Lewis acid is present.

- By varying the substituents at the different positions various types of compounds can be obtained.
- 15 These can be subdivided in the following groups:
1. a borane carbonate compound in which X_1 , X_2 and X_3 are -H and Y is $-OH_2$, and/or the corresponding salts of the mono- or dideprotonated borane carbonate $[H_3BCO_2]^{2-}$;
 2. a borane amino acid (ammonia carboxy borane) in
20 which X_1 is NH_3 , X_2 and X_3 are -H and Y is $-OH$, and/or the corresponding salts of the monodeprotonated ammine borane carbonate $[(NH_3)H_2BCO_2]^-$;
 3. alkylated borane amino acids (trialkyl ammonia carboxy boranes) in which X_1 is $-NH_xR_y$ with $x+y=3$, wherein
25 R is a substituent which is bound by a carbon atom to the nitrogen and is preferably alkyl or aryl, X_2 and X_3 are -H and Y is $-OH$.
 4. compounds of formula I wherein X_1 is an organic substituent bound by a carbon atom to boron, X_2 and X_3 are
30 -H and Y is $-OH_2$.
 5. compounds of formula I wherein X_1 and X_2 are organic substituents bound by a carbon atom to boron, X_3 is -H and Y is $-OH_2$.
 6. borane carboxylic acid alkylester compounds wherein
35 X_1 , X_2 and X_3 are as defined under 1-5 above and Y is OR' , in which R' is a substituent bound by a carbon atom to the oxygen, such as an alkyl, more in particular methyl or ethyl.

7. borane carbamate compounds wherein X_1 , X_2 and X_3 are as defined in 1-5 above and Y is NH_2 , NHR'' or NR''_2 , wherein R'' is a substituent bound by a carbon atom to nitrogen, such as an alkyl, more in particular methyl or ethyl.

Particular examples of these compounds are:
boranocarbonate derivatives: $[H_3B-COOH_2]$, $[H_3B-COOH]M$, $[H_3B-COO]M_2$, $Na[H_3B-COOCH_3]$, wherein M is an alkali cation;
boranocarbamates: $Na[H_3BCONHCH_3]$, $M[H_3B-CONH_2]$, wherein M is an alkali cation;
amine-boranocarbonates: $[H_3N-BH_2-COOH]$, $[H_3N-BH_2-COO]Li$, $[(CH_3)_3N-BH_2-COOH]$, $[(CH_3)_2N-BH_2-COOH]$, $[(CH_3)_2N-BH_2-COO]Li$, $[(CH_3)_2N-BH_2-COOCH_3]$;
amine-boranocarbamates: $[H_3N-BH_2-CONH_2]$, $[(CH_3)_2HN-BH_2-CONHC_2H_5]$

The compounds of the invention can be prepared by means of or analogous to the methods as described by Burg et al., J. Am. Chem. Soc. 59, 780 (1936) for BH_3CO ; Malone et al., Inorg. Chem. 6, 817 (1967) for $M_2[H_3B-COO]$ and $M[H_3B-COOC_2H_5]$; Howe et al., Inorg. Chem. 10, 930 (1971) for $M[H_3B-CONH_2]$; Spielvogel et al., J. Am. Chem. Soc. 102, 6343 (1980) for $[H_3N-BH_2-COOH]$ and $[(CH_3)_3N-BH_2-CONHC_2H_5]$; Spielvogel et al., Inorg. Chem. 23, 4322 (1984) for $[(CH_3)_2N-BH_2-COOCH_3]$; Spielvogel et al., Inorg. Chem. 23, 1776 (1984) and J. Am. Chem. Soc. 98, 5702 (1976) for $[H_3N-BH_2-CONH_2]$, $[(CH_3)_2HN-BH_2-CONHC_2H_5]$.

The invention further relates to a method for preparing transition metal carbonyl complexes, wherein one or more of the compounds defined above are used as the CO source and optionally as the reducing agent. This method comprises in summary the release of CO from any compound of the invention, in particular from one or more of the compounds 1-7, in water or buffer due to protolysis and subsequent hydrolytic reactions.
Concomitantly, the metal with which a carbonyl should be formed is reduced by the hydride substituent attached to boron. The compounds of the invention, in particular compounds 1-7, are dissolved in water or buffer and the

metal is added either as a solid or as a solution. Protonation and hydrolysis of the compounds of the invention, in particular of compounds 1-7, releases CO. At the same time, the hydrides attached to the boron (-H) will reduce the metal center to a valency where the metal is able to coordinate the released CO. In that moment, carbonyl complexes are formed. The method according to the invention for preparing carbonyl complexes, thus comprises mixing the borano compounds of the invention with an aqueous solution of the metal in the form of a metal-ion or (per)metallate. "Metal" as used in this application is intended to encompass all forms of the metal, i.e. also metal ions and (per)metallates.

The compounds and method of the invention are suitable for the formation of any carbonyl complex, but in particular those in which the transition metal in the transition metal carbonyl complex is selected from the groups V-B to VIII-B metals. More in particular the method is suitable for preparing carbonyl complexes of the following transition metals: Vanadium (V), Chromium (Cr), Molybdenum (Mo), Tungsten (W), Manganese (Mn), Technetium (Tc), Rhenium (Re), Iron (Fe), Ruthenium (Ru), Osmium (Os), Cobalt (Co), Rhodium (Rh), Iridium (Ir) and Nickel (Ni) and their radioactive isotopes.

Furthermore, the invention provides a kit for preparing transition metal carbonyl complexes, comprising a compound according to the invention in aqueous solution, a stabilizing agent like tartrate, glucoheptonate, lactate, citrate and a buffer system like borate or phosphate. In a preferred embodiment thereof, the kit of the invention contains at least 2 mg borane carbonate, preferably in a borate buffer (pH 9.1) in an oxygen-free environment under a nitrogen atmosphere. It is preferred that the total volume of the solution after addition of the radioactive metal solution does not exceed 1 ml. However, larger volumes such as 2 or 3 ml may also be useful in certain circumstances. Suitable

incubation conditions comprise heating the solution for about 20 minutes to 75°C.

The compounds of the invention can furthermore be used in water for the reduction of organic compounds with a selectivity and reactivity comparable to boron hydride or cyanoborohydride.

In addition, it was found that H_3BCO can be prepared continuously from $H_3B \cdot THF$ and reacted in situ with an alcoholic solution of potassium hydroxide to give $K_2[H_3BCO_2]$. The key to the preparation is the control of the equilibrium between H_3BCO and $H_3B \cdot THF$: THF is selectively condensed from the gas stream at -50°C, while H_3BCO (b.p. -64°C) passes on, carried by a stream of carbon monoxide. Subsequently, this gas mixture is directly bubbled through an ethanolic solution of KOH at -78°C. Nucleophilic attack of $[OH^-]$ at the highly electrophilic carbon in H_3BCO leads to the formation of $K_2[H_3BCO_2]$ in high yield. If required H_3BCO itself can be isolated in a cold trap at -78°C. This method of preparing H_3BCO is simpler and more convenient than the high pressure or ether-catalyzed procedures and can be scaled up to quantities of several grams or larger.

Thus, the invention relates to method for the preparation of borano carbonate, comprising the steps of:

a) reacting $BH_3 \cdot THF$ or a similar adduct in THF or a mixture of THF and another organic aprotic solvent with CO to generate H_3BCO ;

b) passing the H_3BCO thus generated through a cold solution of a hydroxide with a mono or dikationic counter ion and an aliphatic alcohol; and

c) after a suitable reaction time heating the alcoholic solution to precipitate the borano carbonate. The similar adduct is for example $H_3B(Et_2O)$. The hydroxide is for example selected from the group consisting of potassium hydroxide, sodium hydroxide or tetraalkyl ammonium hydroxide. The aliphatic alcohol can be selected from the group consisting of methanol, ethanol and isopropanol.

The compound H_3BCO is also part of this invention. It has reducing properties and can be used for that purpose for example in the preparation of carbonyl complexes without high pressure CO as described above but then in aprotic or only weakly protic solvents. It is also possible to use H_3BCO in situ while it is produced when CO is bubbled through THF solutions of "metals", such as for the synthesis of the macroscopic $[TcCl_3(CO)_3]_2$ or Re analogue.

10 The use of the compounds according to the invention is more broadly applicable than solely for the preparation of carbonyl complexes, but can also be applied in other circumstances wherein a CO source in aqueous solution is required. The invention also relates to the use of borano carbonate or derivatives thereof as a reducing agent for organic substrates, such as esters, imines or aldehydes, in water. The reducing power of these compounds is comparable to BH_4^- or cyanoborohydride and they can thus be a substitute for e.g. cyanoborohydride in bulk industrial processes.

20 The present invention is further illustrated in the following examples, that are given for illustration purposes only.

25

EXAMPLES

EXAMPLE 1

Preparation of $K_2H_3BCO_2$

1. Synthesis of $BH_3 \cdot CO$

30 4 g of $NaBH_4$ was carefully added to 15 ml of concentrated H_3PO_4 (dried overnight under high vacuum at room temperature) in vacuo (1 mbar) under vigorous stirring over a period of 2 hours. The evolving BH_3 was dried by passing it through a cool trap at $-78^\circ C$ and was condensed in a second cool trap at $-200^\circ C$ containing 70 ml of dry DME. The second trap was disconnected from the first trap and the vacuum line. The temperature was brought to $-40^\circ C$. Subsequently the trap was pressurized

with 1.3 bar of dry CO. The reaction mixture was stirred in a cool bath at -40°C (dry ice with acetonitrile) under 1.3 bar of CO overnight.

5 2. Synthesis of $\text{K}_2\text{H}_3\text{BCO}_3$

The gas outlet of the trap was connected to a 100 ml two-neck round-bottom flask (equipped with gas inlet and reflux condenser) containing 50 ml of dry ethanol and 3 g KOH. The cool bath of the trap was removed and the evolving $\text{BH}_3 \cdot \text{CO}$ was bubbled slowly through the ethanolic KOH solution at 0°C . The DME solution was slowly heated to 80°C and the trap subsequently three times flushed with CO. After the evolution of $\text{BH}_3 \cdot \text{CO}$ had stopped the ethanolic solution was refluxed for 30 min. After cooling the solution to room temperature $\text{K}_2\text{H}_3\text{BCO}_2$ precipitated as a white powder which was filtered by a sintered glass filter, washed with ice cold ethanol and dried under vacuum.

20

EXAMPLE 2

Labeling experiment using a lyophilized kit

A labeling kit was prepared by lyophilizing 1 mg $\text{K}_2[\text{BH}_3\text{COO}]$ in 0.1 ml of 0.1M PBS, pH 7.5 in a vial that was flushed with N_2 . As an alternative a 0.1M borate buffer, pH 8.5 can be used.

For labeling, 1 ml of a generator eluted $[\text{}^{99\text{m}}\text{TcO}_4]^-$ saline solution is added. It was found that the yield is independent of the absolute amount of $[\text{}^{99\text{m}}\text{TcO}_4]^-$. The solution thus obtained is heated to 75°C for 20 min.

The yields are between 80 and 100% (trace 1 in Fig. 1) for pH 7.5; trace 3 in Fig. 1 for pH 8.5.

To establish the identity of the compound, picolinic acid was added directly to the reaction solution, in which the carbonyl complex had been prepared. HPLC revealed the complex $[\text{}^{99\text{m}}\text{Tc}(\text{OH}_2)(\text{pic})(\text{CO})_3]$ (Fig. 1, trace 2) by comparison with "cold" material, in the present case the same complex made with "cold"

Rhenium. The "hot" material is found by means of a radioactivity detector, whereas the "cold" material is detected with a UV detector.

5

EXAMPLE 3Labeling experiment with a so-called "wet kit"

A vial containing 2 mg borane carbonate and a generator eluate of pertechnetate in borate buffer, pH
10 9.1, in a total volume of 1 ml was heated for 20 min. to 75°C. The labeling yield of the product $[^{99m}\text{Tc}(\text{OH})_2(\text{CO})_3]^+$ thus obtained was higher than 97%.

15 **EXAMPLE 4**Preparation of potassium hydrogen (carboxylato)-trihydroborate starting from $\text{H}_3\text{B}\cdot\text{THF}$

The apparatus used consisted of a 250 ml three-necked round-bottomed flask, connected to a cold-trap by
20 a glass tube. The other two necks of the flask were sealed with rubber septa. A PTFE tube for the introduction of gas passed into the flask. From the outlet of the cold-trap, a PTFE tube passed into a 400 ml Schlenk tube. From the side-arm of the Schlenk tube
25 passed a polytene tube leading to a silicone oil bubbler, which isolated the apparatus from the atmosphere.

The cold-trap and the Schlenk tube were immersed in Dewar flasks containing isopropanol. The apparatus was flushed with dry oxygen-free nitrogen for
30 30 minutes while the cold trap was cooled to -50°C and the Schlenk tube to -78°C by addition of dry ice to the respective Dewar flasks.

A solution of 5.0 g potassium hydroxide in 200 ml absolute ethanol was added to the Schlenk tube and
35 allowed to cool to -78°C. The apparatus was briefly flushed with carbon monoxide, and 30 ml of a 1 mol dm⁻³ solution of borane-tetrahydrofuran complex in tetrahydrofuran was introduced into the round-bottomed

flask. Carbon monoxide was bubbled into the solution so that approximately one bubble per second left the apparatus via the oil bubbler. The temperature of the middle cold-trap was maintained at between -45°C and -55°C by occasional addition of dry ice.

After two hours passage of carbon monoxide, 20 ml dimethoxyethane was introduced into the round-bottomed flask and an additional 20 ml dimethoxyethane was introduced into the middle cold-trap. Carbon monoxide was passed through the apparatus as before. After one hour, the Schlenk tube was disconnected from the rest of the apparatus, and allowed to warm to room temperature. The alcoholic solution was heated under reflux for 45 minutes. The resulting white precipitate was filtered off, washed with two 5 ml portions of absolute ethanol, and dried in vacuo to give 1.26 g product (43% based on $\text{BH}_3\cdot\text{THF}$) as a white powder. Found K, 38.85% (gravimetric as $\text{K}_2\text{Na}[\text{Co}(\text{NO}_2)_6]$); CH_4BKO_2 requires K, 39.9%. δ_{H} (200 MHz, D_2O , 25°C) 0.80 (1:1:1:1 quartet, $^1\text{J}(\text{H}-^{11}\text{B}) = 80 \text{ Hz}$; 1:1:1:1:1:1:1 septet, $^1\text{J}(\text{H}-^{10}\text{B}) = 27 \text{ Hz}$).

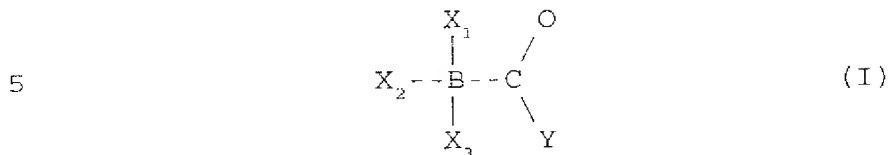
EXAMPLE 5

Reduction of the organic substrate sodium benzaldehyde-2-sulfonate with boranocarbonate in water

Potassium boranocarbonate (100 mg) and sodium benzaldehyde-2-sulfonate (40 mg) were mixed in water (1 ml) and left to stand for 30 min at room temperature. Quantitative formation of sodium 2-(hydroxymethyl)-benzene sulfonate was confirmed by the disappearance of the ^1H -NMR signal of the starting material at $\delta = 10.77$, and the appearance of the product signal at $\delta = 5.04$. The reaction mixture was odorless at the end of the experiment, indicating that the sulfonate group had not been reduced.

CLAIMS

1. Compounds of formula I



wherein X_1 , X_2 and X_3 are the same or different and either
 10 a Lewis base or hydride and Y is a sigma donating group.

2. Compounds as claimed in claim 1, wherein:

X_1 is -H;

X_3 and X_2 are substituents which may be the same or
 different and are selected from the group consisting of
 15 -H, $-\text{NH}_x\text{R}_y$ with $x+y=3$, or -R, wherein R is a substituent
 which is bound by a carbon atom to the nitrogen or boron,
 respectively, and is preferably alkyl or aryl;

Y is -OH, $-\text{OH}_2$, -OR or -NHR, wherein R is a substituent
 which is bound by a carbon atom to the nitrogen or
 20 oxygen, respectively, and is preferably an alkyl or aryl,
 or salts thereof

for use as a carbon monoxide (CO) source and optionally
 as a reducing agent in the preparation of metal carbonyl
 complexes in aqueous solution.

25 3. Compound as claimed in claim 1 or 2 wherein
 the compound is a borane carbonate compound in which X_1 ,
 X_2 and X_3 are -H and Y is $-\text{OH}_2$, and/or the corresponding
 salts of the mono- or dideprotonated borane carbonate
 $[\text{H}_3\text{BCO}_2]^{2-}$.

30 4. Compound as claimed in claim 1 or 2 wherein
 the compound is a borane amino acid (ammonia carboxy
 borane) in which X_1 is NH_3 , X_2 and X_3 are -H and Y is -OH,
 and/or the corresponding salts of the monodeprotonated
 ammine borane carbonate $[(\text{NH}_3)_2\text{H}_2\text{BCO}_2]^-$.

35 5. Compounds as claimed in claim 1 or 2 wherein
 the compounds are alkylated borane amino acids (trialkyl
 ammonia carboxy boranes) in which X_1 is $-\text{NH}_x\text{R}_y$ with $x+y=3$,
 wherein R is a substituent which is bound by a carbon

atom to the nitrogen and is preferably alkyl or aryl, X_2 and X_3 are -H and Y is -OH.

6. Compound as claimed in claim 1 or 2 wherein X_1 is an organic substituent bound by a carbon atom to boron, X_2 and X_3 are -H and Y is $-OH_2$.

7. Compounds as claimed in claim 1 or 2 wherein X_1 , X_2 and X_3 are as defined in claims 2-6 and Y is OR' , in which R' is a substituent bound by a carbon atom to the oxygen, in particular an alkyl, more in particular methyl or ethyl.

8. Compounds as claimed in claim 1 or 2 wherein X_1 , X_2 and X_3 are as defined in claims 2-6 and Y is NH_2 , NHR'' or NR''_2 , wherein R'' is a substituent bound by a carbon atom to nitrogen, in particular an alkyl, more in particular a methyl or ethyl.

9. Compounds as claimed in claim 1 or 2, selected from the group consisting of the boranocarbonate derivatives $[H_3B-COOH_2]$, $[H_3B-COOH]M$, $[H_3B-COO]M_2$, $Na[H_3B-COOCH_3]$, wherein M is an alkali cation; the boranocarbamates $Na[H_3BCONHCH_3]$, $M[H_3B-CONH_2]$, wherein M is an alkali cation; the ammine-boranocarbonates $[H_3N-BH_2-COOH]$, $[H_3N-BH_2-COO]Li$, $[(CH_3)_3N-BH_2-COOH]$, $[(CH_3)_2N-BH_2-COOH]$, $[(CH_3)_2N-BH_2-COO]Li$, $[(CH_3)_2N-BH_2-COOCH_3]$ and the ammine-boranocarbamates $[H_3N-BH_2-CONH_2]$, $[(CH_3)_2HN-BH_2-CONHC_2H_5]$.

10. Method for preparing transition metal carbonyl complexes, wherein one or more compounds as claimed in claims 1-13 are used as the CO source and optionally as the reducing agent.

11. Method as claimed in claim 10, wherein the transition metal in the transition metal carbonyl complex is selected from the groups V-B to VIII-B metals.

12. Method as claimed in claim 11, wherein the transition metal in the transition metal carbonyl complex is selected from the group consisting of Vanadium (V), Chromium (Cr), Molybdenum (Mo), Tungsten (W), Manganese (Mn), Technetium (Tc), Rhenium (Re), Iron (Fe), Ruthenium (Ru), Osmium (Os), Cobalt (Co), Rhodium (Rh), Iridium (Ir) and Nickel (Ni).

13. Kit for preparing transition metal carbonyl complexes, comprising at least one compound according to claims 1-9 in aqueous solution, optionally one or more stabilizers, optionally one or more additional reducing agents and a buffer system.

14. Kit as claimed in claim 13, wherein the stabilizers are selected from the group consisting of glucoheptonate, tartrate, citrate, lactate.

15. Kit as claimed in claim 13 or 14, wherein the additional reducing agents are selected from the group consisting of boron hydrides, dithionites, SnCl_2 , sulfite.

16. Method for the preparation of borano carbonate, comprising the steps of:

15 a) reacting $\text{BH}_3 \cdot \text{THF}$ or a similar adduct in THF or a mixture of THF and another organic aprotic solvent with CO to generate H_3BCO ;

b) passing the H_3BCO thus generated through a cold solution of a hydroxide with a mono or dikationic counter ion and an aliphatic alcohol; and

20 c) after a suitable reaction time heating the alcoholic solution to precipitate the borano carbonate.

17. Method as claimed in claim 16, wherein the similar adduct is $\text{H}_3\text{B}(\text{Et}_2\text{O})$.

25 18. Method as claimed in claim 16 or 17, wherein the hydroxide is selected from the group consisting of potassium hydroxide, sodium hydroxide or tetraalkyl ammonium hydroxide.

19. Method as claimed in claim 16 or 17, 30 wherein the aliphatic alcohol is selected from the group consisting of methanol, ethanol and isopropanol.

20. Method as claimed in claims 16-19, wherein the method is performed as described in example 4.

21. Use of H_3BCO as a reducing agent.

35 22. Use of borano carbonate or derivatives thereof as a reducing agent for organic substrates, such as esters, imines or aldehydes, in water.

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/EP 00/09856

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07F5/02 C07F19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 48848 A (MALLINCKRODT MEDICAL, INC.) 5 November 1998 (1998-11-05) the whole document -----	1-12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex

* Special categories of cited documents:

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Date of the actual completion of the international search

31 January 2001

Date of mailing of the international search report

13/02/2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int: ional Application No

PCT/EP 00/09856

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9848848 A	05-11-1998	EP 0879606 A	25-11-1998
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		EP 1019095 A	19-07-2000
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		PL 336382 A	19-06-2000
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